

# Is Cytoreductive Surgery Possible in Cervical Cancer Peritoneal Carcinomatosis?

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## ABSTRACT

**BACKGROUND:** The number of cases of cervical cancer with recurrence and peritoneal carcinomatosis is limited. In our study, we aimed to present the results of cytoreductive surgery hyperthermic intraperitoneal chemotherapy treatment and its 3-year early period results in patients with peritoneal metastases due to cervical cancer.

**METHODS:** Data of 306 patients who had undergone cytoreductive surgery hyperthermic intraperitoneal chemotherapy between May 2016 and 2021 because of intra-abdominal metastases were collected prospectively and evaluated retrospectively. Ten cases who had undergone cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy due to cervical peritoneal carcinomatosis were included in this study.

**RESULTS:** Average time of operation was 5 (range = 3–6) hours, mean average of peritoneal carcinomatosis index score was 12.3 (range = 7–36), and mean average of completeness of cytoreduction score was 1 in 2 patients and 0 in 8 patients. No mortality was recorded in 30 days postoperatively. Four patients relapsed and died because of pneumonia, coronavirus disease, pulmonary embolism, and terminal illness. These patients died at 2, 5, 6, and 12 months, respectively. Six patients are still alive and early period tumor relapse has not been reported during their follow-ups.

**CONCLUSIONS:** This study has a limited number of patients and the results are early period results. The follow-up of patients were not long term. Therefore, it is hard to say that cytoreductive surgery hyperthermic intraperitoneal chemotherapy could be of any benefit looking at the results. Long-term results should be waited. Also, multicentered randomized cohort study with large sample size is required to evaluate this invasive procedure.

**KEYWORDS:** Cervical cancer, peritoneal carcinomatosis, cytoreductive surgery, intraperitoneal chemotherapy, hyperthermia

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## Introduction

Cancers with peritoneal carcinomatosis (PC) are associated with poor prognosis and are often treated palliatively.<sup>1</sup> Since its first description by Spratt et al in 1980, the treatment of PC by cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) has demonstrated a survival benefit for many indications while proving ineffective for others.<sup>2–6</sup> In the existing treatment of cervical cancer (CC), patients with distant metastases (visceral, parietal layers, and lymph nodes nodal) have been offered combination chemotherapy (CT) with radiotherapy (RT). In the first step of treatment, addition of bevacizumab to carboplatin/paclitaxel or cisplatin/paclitaxel is suggested. Brachytherapy and definitive CT are used in cancers with limited distant metastases localized to the paraaortic lymph nodes. In early-stage cancer, surgery followed by chemoradiotherapy (CRT) is another treatment modality. In palliative treatment, combination CT with taxane/platinum ± bevacizumab is suggested.<sup>7</sup>

Surgery is neglected in cases with recurrence, positive peritoneal cytology, or in cases with PC, which do not have extra-abdominal metastases unless these cases are complicated with

rectovaginal and rectovesical fistulas. In these cases, ileostomy, colostomy, or urological treatment, such as ileal conduit or nephrostomy, is used.

In the last 2 decades, CRS + HIPEC treatment is used in pseudomyxoma peritonei and peritoneal mesothelioma along with ovary, gastric, and colon cancers. Furthermore, because of the success of CRS + HIPEC, its usage has been investigated in other organ cancers, such as sarcomas, breast cancer, cholangiocarcinoma, desmoplastic small round cell tumor, gastrointestinal stromal tumor, hepatocellular carcinoma, pancreas, ovarian cancer, and endometrial cancer. In these rare kinds of cancers, CRS + HIPEC treatment is safe and effective in patients with PC from rare cancer sites of origin.<sup>8</sup>

The number of cases of CC with recurrence and PC is limited. The CRS and HIPEC should be considered in patients with recurrence, positive intra-abdominal cytology, and in whom pelvic exenteration is needed. Usage of medical and radiation oncology units as the first step has become a common approach in cervical PC (CPC) because of the effectiveness of CRT and difficulty of dissection of metastatic lymph nodes



and debulking surgery along with the uncertainty regarding the effectiveness of this surgery. In our study, we aimed to present the results of CRS and HIPEC treatment and its 3-year early period results in patients with PC due to CC limited to the abdomen, without extra-abdominal metastases.

## Materials and Methods

Between May 2016 and 2021, in Ümraniye Training and Research Hospital Surgical Oncology Clinic, data of 306 patients who had undergone CRS and HIPEC surgery because of intra-abdominal metastases were collected prospectively and evaluated retrospectively. Written informed consent was obtained from the study participants and the ethics committee of Ümraniye Training and Research Hospital approved the study (numbered 2021/220). There were 12 cases with PC due to CC recorded in surgical oncology clinic system. Two cases were excluded from the study because of vertebra and supraclavicular lymph node metastases. Ten cases who had undergone CRS and HIPEC due to cervical PC were included in this study. These 10 cases underwent a total of 13 surgeries in different time periods. Among these, 3 cases were excluded from the study owing to relapse of the cancer and HIPEC was not used in these cases. Demographic data of the cases, such as age, comorbidities, American Society of Anesthesiologists (ASA) score, Eastern Cooperative Oncology Group score, body surface area (BSA), previous CRT story, duration of surgery, peritoneal carcinomatosis index (PCI), completeness of cytoreduction (CCS) score, fluid resuscitation perioperatively, the need of erythrocyte suspension and fresh frozen plasma, amount of urine, and duration of intensive care unit (ICU) and hospital stay, were evaluated in terms of postoperative morbidity-mortality and short-term overall survival. All patients were operated with the approval of multidisciplinary tumor council.

### Cytoreductive surgery

Various prognostic scoring systems are needed for patient selection for this highly invasive surgery. PCI is the most commonly used one today. The lower the score, the higher the survival. The main purpose here is to provide R0 resection, which is not to leave a tumor behind macroscopically. Contraindications for CRS and HIPEC include extra-abdominal metastases, low Karnofsky performance scores, and severe cardiac, pulmonary, hepatic, or renal dysfunctions. In addition, extensive small bowel, mesenteric involvement, multiple liver metastases, and paraaortic lymph node involvement are also considered as a contraindication as they do not contribute to the survey.<sup>9</sup>

Complete blood count, biochemistry, tumor markers, chest computed tomography, positron emission tomography/computed tomography, and diffusion-weighted magnetic resonance imaging (MRI) of the patients were evaluated preoperatively. During the operation, modified lithotomy position was used. Midline incision was made starting from the xiphoid process in the pubis. After the incision, PCI score was calculated. All the

tumoral masses in pelvic area and in other sites of the abdomen were excised. In cases with bladder invasion, urology specialist was invited to the operation. All of the cases were relapse cases with intra-abdominal and pelvic metastases, which were pre-operated (total abdominal hysterectomy + bilateral salpingo-oophorectomy [TAH + BSO]) due to CC and, therefore, were operated by the surgical oncology clinic. Anastomoses were made before HIPEC. In addition, anastomoses of ileal conduit, ileostomy, colostomy, and coloanal anastomoses were made before HIPEC.

### HIPEC

HIPEC surgical drainages were placed in the bilateral subdiaphragmatic areas, epigastric area, and pelvic areas. The abdomen was sutured after the placement of heat probes in the pelvic and epigastric areas. Immediately after the abdominal closure, cisplatin (75 mg/m<sup>2</sup> BSA) + doxorubicin (15 mg/m<sup>2</sup> BSA) in 0.9% NaCl solution was injected intra-abdominally and intraperitoneally in 43 and 1200 cc/h turns for 60 minutes. During this procedure, intra-abdominal body temperature was measured using a probe placed in the esophagus by the Belmont Hyperthermia Pump (Belmont Instrument Corporation, Billerica, MA, USA). After the procedure, the patients were transferred to the ICU.

### Statistical analyses

The data obtained from raw data were recorded to IBM SPSS Statistics 22 (IBM SPSS, Turkey) software and analyzed. The numerical data obtained were summarized in tables as arithmetic mean  $\pm$  standard deviation, minimum, maximum, and range values. The nominal and ordinal data were evaluated as frequency and percentages. Finally, overall survival calculated by using Kaplan-Meier survival analysis available in the same software.

## Results

All the patients included in this study were diagnosed and operated at other centers outside our hospital. During the follow-up of these patients, only 2 of the patients had high cancer antigen (CA) 125 level, whereas all the other patients had normal  $\alpha$ -fetoprotein, carcinoembryonic antigen, CA 19-9 levels. A total of 3 cases had rectovaginal fistula and 3 cases had hydronephrosis. Three cases had ended CRT because of inconsistency. Intra-abdominal relapse and PC was reported in abdominal and pelvic MRIs of all of the patients.

CRS and HIPEC was applied to total of 10 patients with cervical PC. During the follow-ups of these patients, 2 of the patients were reoperated due to tumor relapse. One patient had undergone CRS for 2 more times and the other patient had undergone CRS for 1 more time. The HIPEC was not applied to these cases. The mean age of these patients was 52.9 (range = 36-71) years, mean average of ASA scores was 1.9 (range = 1-3), mean BSA was 1.7 (range = 1.5-2) m<sup>2</sup>, mean Karnofsky

**Table 1.** Demographic data of patients.

Age (years)	52.9 ± 12.25
ASA	2 (1-3)
Karnofsky score	88 ± 13.16
BSA	174.7 ± 16.17
Preoperative chemotherapy	9 (%90)
Hospitalization day	15.1 (4-67)
Preoperative symptoms	
Rectovaginal fistula	3 (30%)
Rectovesical fistula	2 (20%)
Hydroureteronephrosis	3 (30%)

Abbreviations: ASA, American Society of Anesthesiologists; BSA, body surface area.

Data are expressed as mean ± standard deviation and n (%).

performance score was 88 (range = 80-100), and average stay at the hospital was 15.1 (range = 4-67) days (Table 1). The average time of operation was 5 (range = 3-6) hours, mean average of PCI score was 12.3 (range = 7-36), mean average of CCS was 1 in 2 patients and 0 in 8 patients. The average number of anastomoses of the colon and small intestine was 1.5 (range = 0-3). Preoperatively, all patients were resuscitated with an average amount of 3200 (range = 2500-4500) cc crystalloids, 500 (range = 300-1000) cc colloid, 1.1 units (range = 0-4) of erythrocyte suspension, and 8 units (range = 0-2) of fresh frozen plasma. An average amount of 550 (range = 200-1100) cc of urine and 630 (range = 200-2400) cc of bleeding was reported (Table 2). Along with excision of peritoneum, lymph nodes, and intestine resections, 5 of the cases also had partial bladder excision and primary suturation, 4 cases had partial ureter resection and ureteroneocystostomy, 3 cases had total cystectomy + ileal conduit, 1 case had abdominoperineal resection, 1 case had coloanal anastomosis, and 1 case had pubic bone excision. One case also had gastric metastases; therefore, total gastrectomy was also added to the procedure. Double J catheters were removed after 6 weeks. Four cases had loop ileostomy and fermeture was applied to 1 of the loop ileostomies. Four cases had end ileostomy and fermeture was not applied to these cases. Two cases underwent end colostomy (Table 3). Intraperitoneal chemotherapy consisting of cisplatin and doxorubicin was applied to all the cases for 60 minutes after the suturation of the abdomen. Major complication related to chemotherapy was not recorded.

During the postoperative period, grade 3 complication according to Clavien-Dindo (CD) classification was recorded in 5 cases (50%). One colorectal anastomosis leak (CD grade 3b) was recorded and Hartmann end colostomy was applied in this case, and 1 ileum anastomosis leak was recorded (CD grade 3b) and end ileostomy was applied in this case. One

**Table 2.** Preoperative findings.

Operation time (hour)	5 (3-6)
PCI score	12.3 (7-36)
Residual tumor CC	
CC-0 (no residual nodules)	2 (20%)
CC-1 (residual < 2.5 mm)	8 (80%)
Number of anastomoses	1.5 (0-3)
Preoperative fluid	
Crystalloid	3200 (2500-4500)
Colloid	500 (300-1000)
Erythrocyte suspension	1.1 (0-4)
Fresh frozen plasma	0.8 (0-4)
Urine	550 (200-1100)
Hemorrhage	630 (200-2400)

Abbreviations: CC, completeness of cytoreduction; PCI, peritoneal carcinomatosis index.

evisceration was recorded (CD grade 3a) and it was treated with primary suturation of the abdomen under local anesthesia, and 1 esophagojejunostomy leak (CD grade 3a) was recorded and it was treated with endoscopic stent. One bladder urine leak (CD grade 3a) was recorded and it was treated with placement of percutaneous drainage catheter placement intra-abdominally and Foley catheter placement for 21 days. The leak ended spontaneously (Table 4).

No mortality was recorded in 30 days postoperatively. Four patients relapsed and died because of pneumonia, coronavirus disease, pulmonary embolism, and terminal illness. These patients died at 2, 5, 6, and 12 months, respectively. Six patients are still alive and early period tumor relapse has not been reported during their follow-ups. Three patients are in their sixth month postoperative period, 1 patient is in 11th month, 1 patient is in 15th month, and 1 patient is in 25th month postoperative period (Figure 1).

## Discussion

PC is defined as metastasis of intra-abdominal tumors to the peritoneum. During the last 2 decades, it was considered as an incurable disease until the developments in CRS and HIPEC treatment and also demonstration of effectiveness of this treatment in aggressive diseases, such as pseudomyxoma peritonei and peritoneal mesothelioma. The CRS and HIPEC has been a light of hope for this patient group.<sup>9,10</sup>

CRS and HIPEC treatment is used extensively by surgeons in the last stage colon, ovary, and gastric cancer and countless clinical studies are presented. However, no definite consensus has been reached regarding the effectiveness of CRS and HIPEC.

**Table 3.** Organ resections.

Partial bladder excision and primary closure	5 (50%)
Partial ureter resection and ureteroneocystostomy	4 (40%)
Total cystectomy + ileal conduit	3 (30%)
Abdominoperineal resection	1
Coloanal anastomosis	1
Partial pubic bone excision	1
Total gastrectomy	1
Stoma status	
Loop ileostomy	4 (40%)
End ileostomy	4 (40%)
End colostomy	2 (20%)

Based on these positive results, CRS and HIPEC treatment has been applied with success in rare cancers, such as sarcomas, breast cancer, cholangiocarcinoma, desmoplastic small round cell tumor, gastrointestinal stromal tumor, hepatocellular carcinoma, pancreas, ovarian cancer, and endometrium cancer. In addition, the role of HIPEC in carcinosarcomas is still being evaluated and there are no published data specifically for this clinical entity. Similarly, the combination of intravenous and intraperitoneal administration of chemotherapy is a therapeutic choice.<sup>11</sup> CRS and HIPEC treatment modality in CC with PC has been a point of interest in literature because of these advancements in rare cancers.

The usual distant metastasis sites for CC are the lungs, liver, bone, and supraclavicular lymph nodes. However, rare sites, such as ovary and peritoneum, are also reported.<sup>12,13</sup> The possible mechanism for PC includes direct, hematogenous, lymphatic, or transtubal implantation of malignant cells.<sup>14-16</sup> In the recent studies, the etiology of PC of CC has been considered as retrograde menstruation and tumoral cell seeding due to uterus perforation.<sup>17-19</sup>

The 5-year survival rates are 16% for stage IVA and 15% for stage IVB carcinoma.<sup>20</sup> As classical knowledge, in treatment modality for early-stage CC, surgery is considered as a first step treatment. If the lymph nodes are involved, radiation and medical oncology clinics are involved during the treatment. In stage IV tumors, palliative treatment is considered. Treatment options include paclitaxel/cisplatin with bevacizumab, paclitaxel/cisplatin, cisplatin/gemcitabine, cisplatin/topotecan, vinorelbine, or ifosfamide.<sup>21,22</sup> Moreover, there is no evidence to date that secondary care improves overall survival compared with the best supportive care. However, women with this condition are usually symptomatic and relatively young. Treatment options that provide improvement in disease-related symptoms, quality of life, and prolongation of progression-free survival are valuable. A few

**Table 4.** Grade 3 Clavien-Dindo complications classification and management.

COMPLICATION	MANAGEMENT
Leakage in colorectal anastomosis (CD grade 3b)	Hartmann end colostomy
Leakage in ileum anastomosis (CD grade 3b)	End ileostomy
Evisceration (CD grade 3a)	Primary closure
Esophagojejunostomy leak (CD grade 3a)	Endoscopic stent
Bladder leak (CD grade 3a)	Percutaneous drainage catheter
Total	5 (50%)

Abbreviation: CD, Clavien-Dindo.

phase II studies of cytotoxic or targeted agents as second-line therapy have shown response rates typically less than 10%.<sup>23</sup>

CC treatment is primarily the specialty of gynecological oncology specialists. However, approach to preoperated cases, TAH + BSO with intra-abdominal tumor relapses, should be multidisciplinary because of the recurrence seen quite often and urology specialist and surgical oncology specialists should be involved in cases with relapses in the rectum, bladder, ureter, and small intestine. Tumor relapse or peritoneal involvement is usually detected by imaging modalities during the follow-ups of medical oncology or surgical oncology department. Evaluation of peritoneal cytology in detecting recurrence or CPC in CC patients can lead to an earlier diagnosis.

Eskander et al, Ito et al, and Takeshima et al have revealed the importance of positive cytology in their studies. They have shown that 10% of patients can be diagnosed with positive cytology and can be treated with neoadjuvant treatment.<sup>24-26</sup> Furthermore, meta-analysis by Yoon et al<sup>27</sup> indicates that abnormal peritoneal cytology may be strongly associated with poor prognosis in patients with CC.

According to our evaluation, peritoneal cytology may lead to earlier diagnosis in the detection of recurrence or CPC in CC patients. However, this method is not used often by clinicians. As we have already mentioned in this study, we operated on cases who did not receive any medical oncology and radiation oncology treatment or developed complications. We accept that the prognosis is poor, such as stomach cancer, gallbladder, and pancreatic cancer, but even in these tumor types, it has contributed more to survival than medical and radiological oncological treatments. In addition, 20 years ago, these treatments for peritoneal mesothelioma and pseudomyxoma peritonei were a dream and today they are included in the guidelines as the primary treatment. However, it is not possible to conduct a prospective randomized controlled study in stage IV CC cases.

Morrow et al<sup>28</sup> reported aortic and pelvic lymph node metastasis rates of 30% and 50% respectively, in stage 3-4 CC cases in their series.



Overall survival	Survivals, %		
	6-months	9-mo	18-mo
MeanSurvivalMonths (95% CI)			
9,2 (3,66 – 14,73)	58	38	19

**Figure 1.** Overall survival.

Jiménez and Covens<sup>29</sup> have reported that tumor size larger than 8 cm, bilateral pelvic sidewall involvement, hydronephrosis, and lower vaginal involvement are associated with a worse survival and central tumor control rates and these patients are poor candidates for retroperitoneal debulking.

Studies regarding CPC are mainly based on case series in literature.

Boussios et al reported that recurrences may be central pelvic, lateral pelvic, and extra-pelvic. Central pelvic relapse can be located in the vaginal vault or usually involve the bladder and/or rectum. Lateral pelvic recurrence includes parietal and visceral pelvic side disease developed above and below the level of the obturator nerve, respectively. For the vast majority of patients with recurrent or metastatic disease, palliative chemotherapy represents the only treatment option.<sup>30</sup> Burg et al reported in their study that PC in CC is 1%. Ovarian cancers, serous and clear cell endometrial cancers, and adenocarcinoma of the cervix have the highest risk for the occurrence of PC. They have reported that upcoming treatment strategies, such as HIPEC, are promising.<sup>31</sup> Sugarbaker et al<sup>32</sup> have reported that CRS and HIPEC could be successfully applied in CPC in experienced centers in a case series study consisting of 3 cases.

Honoré et al<sup>33</sup> performed CRS + HIPEC on a CPC case in their study and stated that performing these operations on unusual malignancies is still a difficult decision.

Angeles et al<sup>34</sup> have reported that surgery has a salvage role in patients with isolated recurrences after primary treatment with RT or CRT. Davenport et al<sup>35</sup> have reported that in cases with recurrent RT story, primary debulking should not be considered because of the advancements in chemotherapeutic field. On the other hand, Tseng et al<sup>36</sup> have reported that surgery could be an option in selected patient groups with stage IV CC with PC. Fagundes et al<sup>37</sup> have reported local control rate of approximately 50% and pelvic failure rate of 75% in CC.

Wen et al<sup>38</sup> have reported that HIPEC with IP angiogenesis inhibitors is effective and safe for the management of malignant ascites in advanced-stage gynecological and gastrointestinal cancer. Brandl et al reported in their series in which they performed CRS and HIPEC that perioperative morbidity is acceptable in specialized peritoneal surface malignancy (PSM) centers. They have reported that more data are needed to achieve the goal of a better definition of indications in rare PSM.<sup>39</sup>

In our study, of the total 306 cases of CRS and HIPEC, operation owing to the CC was found to be performed in 3.9% cases, which is higher than reported in the literature (1%) because of the fact that 70% of the cases operated in our

surgical oncology clinic were mainly preoperated and complicated (such as rectovaginal and rectovesical fistulas).

We detected that the mean hospital stay for patients who had undergone CRS and HIPEC due to colorectal cancer is 8 days, whereas the mean hospital stay for cervical PC patients is 15 days. In patients with colorectal cancer, complication rate was 10% when morbidity score was 3 or higher according to CD classification, whereas in CPC complication rate detected was 50%. This high complication rate may be because of the complex surgical interventions in the pelvic area and high morbidity levels regarding this surgery. We included patients with end-stage CC who developed complications requiring surgical intervention in this study. We believe that our high morbidity rate is related to this. Therefore, we think that our early results are promising in a group of patients in whom nothing can be done, except opening the stoma. We know that in these complicated surgeries, our morbidity-mortality rates will decrease to a more acceptable level with appropriate patient selection.

As our study consisted of a limited number of retrospective cases, it was not possible to determine any statistical significance from this study. This was a limitation for our study. From this retrospective study, by looking at the early-term results in patients with CPC, we think that CRS + HIPEC can be technically performed but it is too early to say that these highly invasive procedures will be of benefit due to both the high complication rate and the short expected overall survival in the early period.

## Conclusions

This study has a limited number of patients and the results are early period results. The follow-up of patients was not long term. Therefore, it is hard to say that CRS + HIPEC could be of any benefit looking at the results. Long-term results should be waited. Also, multicentered randomized cohort study with large sample size is required to evaluate this highly invasive procedure.

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## Author Contributions

OD contributed to concept and design, drafting of the manuscript, and critical revision of the manuscript. MK contributed to interpretation of data and acquisition of data. All authors read and approved the final version of the manuscript.

## Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms.

## Ethics Approval and Consent to Participate

The ethics committee of Ümraniye Training and Research Hospital approved the study (numbered 2021/220).

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